Thus, the lowest concentration where a developmental adverse effect was observed was 500 μg/m^3 from the Dorman *et al.* (2005a) study, based on decreased liver weight. This value, therefore, is the most appropriate value for comparison to the neurological effects NOAEL of 60 μg/m^3 from the occupational studies. As discussed in our publication (Bailey *et al.* 2009), conversion of the rodent developmental LOAEL of 500 μg/m^3 to a human equivalent $NOAEL_{[HEC]}$ results in a value of 32 μg/m^3 for continuous exposure (compared to a value of 21 μg/m^3 for continuous exposure[14] converted from the occupational NOAEL of 60 μg/m^3). In addition, as discussed below, recent pharmacokinetic data suggest that fetal and neonatal Mn brain concentrations were not very different from adult Mn brain concentrations following exposure to 0.05, 0.5, and 1 μg/m^3 Mn in air. These studies provide sufficient evidence to suggest that developmental effects from inhalation of Mn are not more sensitive than neurological effects, and therefore neurological effects remain the most appropriate endpoint for re-evaluation of the Mn RfC.

A.2.4 Recent pharmacokinetic data that are relevant to re-evaluation of the Mn RfC

There have been recent advances in the understanding of the pharmacokinetics of inhaled Mn in potentially sensitive individuals. This has been extensively studied and reviewed by Dorman *et al.* (2004, 2005a,b, 2006a,b) where the authors compared the Mn brain concentrations of healthy young adult male rats to rats that were considered to reflect potentially susceptible subpopulations (aged; abnormal hepatobiliary function; sub-optimal iron or Mn intake; and fetuses, neonates, and children). The authors concluded that inhaled Mn particles result in "qualitatively similar end-of-exposure brain Mn concentrations" in the potentially susceptible subpopulations as compared to healthy young adult male rats.

More recently, physiologically-based pharmacokinetic (PBPK) models for inhaled Mn have been developed which provide a thorough quantitative analysis of Mn tissue concentrations in rats (Teeguarden *et al.*, 2007a,b,c; Nong *et al.*, 2008), including placental transfer to fetuses (Yoon *et al.* 2009a), lactational transfer to pups (Yoon *et al.*, 2009b), and in non-human primates (Nong *et al.*, 2009). Andersen *et al.* (2010) summarized these PBPK models, describing how the models consider ingestion and inhalation kinetics of Mn along with homeostatic control of Mn. In addition, a recent presentation of the Mn PBPK models described a human fetus and neonate model developed by extrapolation from the rat PBPK model (Clewell 2010). As described by Clewell (2010), the human model predicted similar Mn tissue concentrations (from Mn exposure concentrations ranging from 1 to 10 μg/m^3) in the target brain region

[14] See description below.

in the human fetus and nursing infant compared to those in the mother and other adults. Application of these PBPK models to Mn risk assessment is warranted, as described by Andersen *et al.* (2010), Clewell (2010) and others in recent reviews (Santamaria and Sulksy, 2010; Boyes, 2010).

In addition, as described in Andersen *et al.* (2010), the non-human primate PBPK model indicates that the "globus pallidus is not expected to accumulate Mn during exposures below ~10 $\mu g/m^3$, which is well above current Mn RfC and typical environmental levels." Similar results are described by (Clewell 2010) from the human PBPK model. The monkey and human PBPK studies suggest that concentrations below 10 $\mu g/m^3$ Mn in air are not likely to lead to increased Mn brain concentrations in human fetuses, children, and adults. An accumulation threshold for Mn is biologically plausible because Mn is an essential nutrient, and homeostatic control mechanisms limit accumulation of essential nutrients at doses less than an accumulation threshold (Santamaria, 2008). This accumulation threshold should be considered in any inhalation risk assessment for Mn.

A.2.5 Proposed Mn RfC from Bailey *et al.* (2009)

As discussed above, the three most appropriate occupational studies for re-evaluation of the Mn RfC, based on using a NOAEL as a point of departure, are those by Gibbs *et al.* (1999) (NOAEL = 66 $\mu g/m^3$), Deschamps *et al.* (2001) (NOAEL = 57 $\mu g/m^3$), and Young *et al.* (2005) (NOAEL = 58 $\mu g/m^3$). Because these NOAELs are all very close to 60 $\mu g/m^3$, we chose 60 $\mu g/m^3$ as the point of departure for derivation of one Mn RfC. We derived two Mn RfCs, following standard US EPA methodology (US EPA, 1994, 2002): one based on the NOAEL of 60 $\mu g/m^3$, and another based on the 95% lower confidence limit on a benchmark dose associated with 10% extra risk ($BMDL_{10}$)[15] derived by Clewell *et al.* (2003) (200 $\mu g/m^3$). As described in Bailey *et al.* (2009), and based on the studies available at the time, we calculated Mn RfCs of 2 $\mu g/m^3$ (based on the NOAEL) and 7 $\mu g/m^3$ (based on the BMDL). These RfCs were calculated as follows:

First, the points of departure were adjusted to reflect continuous exposure (as opposed to occupational exposure).

$$NOAEL_{[HEC]} = NOAEL \times 5/7 \text{ days} \times 10/20 \text{ m}^3/\text{day} \quad (1)$$
$$BMDL_{[HEC]} = BMDL \times 5/7 \text{ days} \times 10/20 \text{ m}^3/\text{day}$$

[15] The term "BMD" is used here to be consistent with the terminology used by Clewell *et al.* (2003), although it is technically referred to as a Benchmark Concentration (BMC).

Using a NOAEL of 60 $\mu g/m^3$ results in a $NOAEL_{[HEC]}$ = 60 $\mu g/m^3$ x 5/7 days x 10/20 m^3/day = 21 $\mu g/m^3$. Similarly, using the $BMDL_{10}$ of 200 $\mu g/m^3$ derived by Clewell *et al.* (2003) results in a $BMDL_{[HEC]}$ of 71 $\mu g/m^3$.

The RfCs were then calculated based on application of appropriate uncertainty factors (UF):

$$RfC = NOAEL_{[HEC]} \text{ or } BMDL_{10[HEC]}/UFs \quad (2)$$

We applied a UF of 10 for intraspecies variability, based on the data available at the time, leading to an RfC of 2 $\mu g/m^3$ (21 $\mu g/m^3$ / 10) from the NOAEL and 7 $\mu g/m^3$ (71 $\mu g/m^3$ / 10) from the $BMDL_{10}$. As described in Bailey *et al.* (2009), the current data suggest that additional UFs are not necessary for Mn species differences in toxicity or for subchronic exposures. In addition, as discussed above, there is no need to add a UF for developmental effects.

Although the more recent PBPK models discussed here suggest that a UF of 10 may not be necessary for fetuses, neonates, or children, a UF of 10 may still be necessary based on other potentially sensitive subpopulations (aged; abnormal hepatobiliary function; and sub-optimal iron or Mn intake). In addition, given the possibility of a threshold of 10 $\mu g/m^3$, it may not be health protective to derive a Mn RfC that exceeds the threshold value. Our RfCs fall just below the proposed threshold.

A.2.6 Recent draft Mn inhalation toxicity criteria from ATSDR and California EPA

ATSDR and California EPA have recently proposed DRAFT Mn inhalation toxicity criteria (ATSDR, 2008; OEHHA, 2008; Winder *et al.* 2010). These values and their bases are summarized in Table A.2.

Both the ATSDR and California EPA point of departure values (BMCLs of 142 $\mu g/m^3$ and 72 $\mu g/m^3$, respectively) are very similar to those used in our analysis. ATSDR incorporates a UF of 10 to account for intraspecies variability, and another UF of 10 to account for differences in toxicities in different Mn species, database limitations and sensitivities to children, for a total UF of 100, and a draft minimal risk level (MRL) of 0.3 $\mu g/m^3$ (6-fold higher than the current RfC). California EPA applies a UF of 100 for intraspecies variability, and a UF of 3 for use of a subchronic study, for a draft reference exposure level (REL) of 0.09 $\mu g/m^3$ (1.8-fold higher than the current RfC). As discussed above, recent

PBPK models suggest that a UF for sensitivity to children, neonates, and fetuses, is not necessary, and a UF of 10 should be sufficient for other potentially sensitive subpopulations. Further, as discussed in Bailey *et al.* (2009), a UF for different Mn species is also not necessary because the toxicity value is based on the more common environmental form of Mn (*i.e.*, the less soluble Mn oxides, commonly generated from metallurgical processes such as steel production) and therefore would be most generally applicable. It may be appropriate to adjust the toxicity values for more soluble forms of Mn (*e.g.*, Mn sulfates) on a case by case basis. Or, if an adjustment factor is applied to account for differences in toxicity of Mn species, an adjustment should be allowed for exposures to less bioavailable Mn species[16]. Finally, as discussed in our paper (Bailey *et al.* 2009), a UF for use of a subchronic study is not necessary. As described by Clewell *et al.* (2003), analysis of the dose response data for subclinical effects of Mn provides evidence that exposure concentration is the determining factor for the appearance of subclinical effects, and <u>not</u> exposure duration.

Before finalizing these draft toxicity values, ATSDR, California EPA, and other regulatory agencies should consider the recent PBPK models discussed here that: 1) address intraspecies variability and sensitivity to children, neonates, and fetuses; and 2) suggest a potential threshold exists (10 $\mu g/m^3$), likely due to the fact that Mn is an essential metal, below which Mn brain concentrations are not likely to increase in adults, children, neonates, and fetuses.

[16] It is important to point out that the PBPK studies that suggest an accumulation threshold for Mn in the brain of 10 $\mu g/m^3$ were conducted with the more soluble, more bioavailable, and potentially more toxic Mn sulfates (Nong *et al.*, 2009; Andersen *et al.*, 2010).

References

Andersen, ME; Dorman, DC; Clewell, HJ III; Taylor, MD; Nong, A. 2010. "Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment." *J. Toxicol. Environ. Health A.* 73(2):217-234.

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. "Toxicological profile for manganese." 504p., September.

Agency for Toxic Substances and Disease Registry (ATSDR). 2008. "Toxicological Profile for Manganese (Draft)." Accessed on October 23, 2008 at http://www.atsdr.cdc.gov/toxprofiles/tp151.pdf, 539p., September.

Bailey, LA; Goodman, JE; Beck, BD. 2009. "Proposal for a revised Reference Concentration (RfC) for manganese based on recent epidemiological studies." *Regul. Toxicol. Pharmacol.* 55:330-339.

Baldwin, M; Mergler, D; Larribe, F; Belanger, S; Tardif, R; Bilodeau, L; Hudnell, K. 1999. "Bioindicator and exposure data for a population based study of manganese." *Neurotoxicology.* 20(2-3):343-353.

Barnes, DG; Dourson, ML. 1988. "Reference dose (RfD): Description and use in health risk assessment." *Regul. Toxicol. Pharmacol.* 8:471-486.

Bast-Pettersen, R; Ellingsen, DG; Hetland, SM; Thomassen, Y. 2004. "Neuropsychological function in manganese alloy plant workers." *Int. Arch. Occup. Environ. Health.* 77(4):277-287.

Beuter, A; Edwards, R; deGeoffroy, A; Mergler, D; Hudnell, K. 1999. "Quantification of neuromotor function for detection of the effects of manganese." *Neurotoxicology.* 20(2-3):355-366.

Bowler, RM; Mergler, D; Sassine, MP; Larribe, F; Hudnell, K. 1999. "Neuropsychiatric effects of manganese on mood." *Neurotoxicology.* 20(2-3): 367-378.

Boyes, WK. 2010. "Essentiality, toxicity, and uncertainty in the risk assessment of manganese." *J. Toxicol. Environ. Health A.* 73(2):159-165.

Chia, SE; Foo, SC; Gan, SL; Jeyaratnam, J; Tian, CS. 1993. "Neurobehavioral functions among workers exposed to manganese ore." *Scand. J. Work Environ. Health.* 19(4):264-270.

Clewell, HJ; Lawrence, GA; Calne, DB; Crump, KS. 2003. "Determination of an occupational exposure guideline for manganese using the benchmark method." *Risk Anal.* 23(5):1031-1046.

Conolly, RB. 2009. "Commentary on "Toxicity testing in the 21st century: implications for human health risk assessment" by Krewski *et al.*" *Risk Anal.* 29(4):480-481.

Crump, KS; Rousseau, P. 1999. "Results from eleven years of neurological health surveillance at a manganese oxide and salt producing plant." *Neurotoxicology.* 20(2-3):273-286.

Crump, KS. 1998. "On summarizing group exposures in risk assessment: Is an arithmetic mean or a geometric mean more appropriate?" *Risk Anal.* 18(3):293-297.

Deschamps, FJ; Guillaumot, M; Raux, S. 2001. "Neurological effects in workers exposed to manganese." *J. Occup. Environ. Med.* 43(2):127-132.

Dorman, DC; McManus, BE; Marshall, MW; James, RA; Struve, MF. 2004. "Old age and gender influence the pharmacokinetics of inhaled manganese sulfate and manganese phosphate in rats." *Toxicol. Appl. Pharmacol.* 197(2):113-124.

Dorman, DC; McElveen, AM; Marshall, MW; Parkinson, CU; James, RA; Struve, MF; Wong, BA. 2005a. "Tissue manganese concentrations in lactating rats and their offspring following combined in utero and lactation exposure to inhaled manganese sulfate." *Toxicol. Sci.* 84(1):12-21.

Dorman, DC; McElveen, AM; Marshall, MW; Parkinson, CU; Arden James, R; Struve, MF; Wong, BA. 2005b. "Maternal-fetal distribution of manganese in the rat following inhalation exposure to manganese sulfate." *Neurotoxicology.* 26(4):625-632.

Dorman, DC; Struve, MF; Marshall, MW; Parkinson, CU; James, RA; Wong, BA. 2006a. "Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation." *Toxicol. Sci.* 92(1):201-210.

Dorman, DC; Struve, MF; Clewell, HJ; Andersen, ME. 2006b. "Application of pharmacokinetic data to the risk assessment of inhaled manganese." *Neurotoxicology.* 27(5):752-764.

Erikson, KM; Dorman, DC; Lash, LH; Aschner, M. 2005. "Persistent alterations in biomarkers of oxidative stress resulting from combined in utero and neonatal manganese inhalation." *Biol. Trace Elem. Res.* 104(2):151-163.

Gibbs, JP; Crump, KS; Houck, DP; Warren, PA; Mosley, WS. 1999. "Focused medical surveillance: A search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust." *Neurotoxicology.* 20(2-3):299-313.

Goodman, JE; Dodge, DG; Bailey, LA. 2010. "A framework for assessing causality and adverse effects in humans with a case study of sulfur dioxide." *Regul. Toxicol. Pharmacol.* 58:308-322.

Gordis, L. 2008. "Epidemiology." Saunders Elsevier (Philadelphia, PA), 375p.

HaMai, D; Rinderknecht, AL; Guo-Sharman, K; Kleinman, MT; Bondy, SC. 2006. "Decreased expression of inflammation-related genes following inhalation exposure to manganese." *Neurotoxicology* 27(3):395-401.

Haynes, EN; Heckel, P; Ryan, P; Roda, S; Leung, YK; Sebastian, K; Succop, P. 2010. "Environmental manganese exposure in residents living near a ferromanganese refinery in Southeast Ohio: A pilot study." *Neurotoxicology.* 31(5):468-474.

Klaassen, CD; ed. 2008. "Casarett and Doull's Toxicology: The Basic Science of Poisons (Seventh Edition)." McGraw-Hill Companies, Inc. 1309p

Lucchini, R; Apostoli, P; Perrone, C; Placidi, D; Albini, E; Migliorati, P; Mergler, D; Sassine, MP; Palmi, S; Alessio, L. 1999. "Long-term exposure to "low levels" of manganese oxides and neurofunctional changes in ferroalloy workers." *Neurotoxicology.* 20(2-3):287-297.

Lucchini, R; Selis, L; Folli, D; Apostoli, P; Mutti, A; Vanoni, O; Iregren, A; Alessio, L. 1995. "Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure." *Scand. J. Work Environ. Health.* 21(2):143-149.

Mergler, D; Huel, G; Bowler, R; Iregren, A; Belanger, S; Baldwin, M; Tardif, R; Smargiassi, A; Martin, L. 1994. "Nervous system dysfunction among workers with long-term exposure to manganese." *Environ. Res.* 64:151-180.

Mergler, D; Baldwin, M; Belanger, S; Larribe, F; Beuter, A; Bowler, R; Panisset, M; Edwards, R; de Geoffroy, A; Sassine, MP; Hudnell, K. 1999. "Manganese neurotoxicity, a continuum of dysfunction: Results from a community based study." *Neurotoxicology.* 20(2-3):327-342.

Myers, JE; Thompson, ML; Ramushu, S; Young, T; Jeebhay, MF; London, L; Esswein, E; Renton, K; Spies, A; Boulle, A; Naik, I; Iregren, A; Rees, DJ. 2003. "The nervous system effects of occupational exposure on workers in a South African manganese smelter." *Neurotoxicology.* 24(6):885-894.

Nong, A; Teeguarden, JG; Clewell, HJ; Dorman, DC; Andersen, ME. 2008. "Pharmacokinetic modeling of manganese in the rat IV: Assessing factors that contribute to brain accumulation during inhalation exposure." *J. Toxicol. Environ. Health A.* 71(7):413-426.

Nong, A; Taylor, MD; Clewell, HJ; Dorman, DC; Andersen, ME. 2009. "Manganese tissue dosimetry in rats and monkeys: accounting for dietary and inhaled Mn with physiologically based pharmacokinetic modeling." *Toxicol. Sci.* 108(1):22-34.

California, Office of Environmental Health Hazard Assessment (OEHHA). 2008. "Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries." In *Air Toxics Hot Spots Program Technical Support Document For the Derivation of Noncancer Reference Exposure Levels*, p1-238., December.

Riojas-Rodriguez, H; Solis-Vivanco, R; Schilmann, A; Montes, S; Rodriguez, S; Rios, C; Rodriguez-Agudelo, Y. 2010. "Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese." *Environ. Health Perspect.* 118(10):1465-1470.

Rodriguez-Agudelo, Y; Riojas-Rodriguez, H; Rios, C; Rosas, I; Sabido Pedraza, E; Miranda, J; Siebe, C; Texcalac, JL; Santos-Burgoa, C. 2006. "Motor alterations associated with exposure to manganese in the environment in Mexico." *Sci. Total Environ.* 368(2-3):542-556.

Roels, HA; Ghyselen, P; Buchet, JP; Ceulemans, E; Lauwerys, RR. 1992. "Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust." *Br. J. Ind. Med.* 49:25-34.

Santamaria, AB. 2008. "Manganese exposure, essentiality & toxicity." *Indian J. Med. Res.* 128(4):484-500.

Santamaria, AB; Sulsky, SI. 2010. "Risk assessment of an essential element: Manganese." *J. Toxicol. Environ. Health A.* 73(2):128-155.

Santos-Burgoa, C; Rios, C; Mercado, LA; Arechiga-Serrano, R; Cano-Valle, F; Eden-Wynter, RA; Texcalac-Sangrador, JL; Villa-Barragan, JP; Rodriguez-Agudelo, Y; Montes, S. 2001. "Exposure to manganese: Health effects on the general population, a pilot study in central Mexico." *Environ. Res.* 85:90-104.

Solis-Vivanco, R; Rodriguez-Agudelo, Y; Riojas-Rodriguez, H; Rios, C; Rosas, I; Montes, S. 2009. "Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese." *Environ. Toxicol. Pharmacol.* 28(2):172-178.

Standridge, JS; Bhattacharya, A; Succop, P; Cox, C; Haynes, E. 2008. "Effect of chronic low level manganese exposure on postural balance: A pilot study of residents in southern Ohio." *J. Occup. Environ. Med.* 50:1421-1429.

Strawson, J; Zhao, Q; Dourson, M. 2004. "Reference dose for perchlorate based on thyroid hormone change in pregnant women as the critical effect." *Regul. Toxicol. Pharmacol.* 39(1):44-65.

Teeguarden, JG; Dorman, DC; Covington, TR; Clewell, HJ; Andersen, ME. 2007a. "Pharmacokinetic modeling of manganese. I. Dose dependencies of uptake and elimination." *J. Toxicol. Environ. Health A.* 77(18):1493–1504.

Teeguarden, JG; Dorman, DC; Nong, A; Covington, TR; Clewell, HJ; Andersen, ME. 2007b. "Pharmacokinetic modeling of manganese. II. Hepatic processing after ingestion and inhalation." *J. Toxicol. Environ. Health A.*. 77(18):1505–1514.

Teeguarden, JG; Gearhart, J; Clewell, HJ; Covington, TR; Nong, A; Andersen, ME. 2007c. "Pharmacokinetic modeling of manganese. III. Physiological approaches accounting for background and tracer kinetics." *J. Toxicol. Environ. Health A.* 70(18):1515–1526.

US EPA. 1990. "General Quantitative Risk Assessment Guidelines for Noncancer Health Effects (Review draft)." Report to US EPA, Risk Assessment Forum, Technical Panel for the Development of Risk Assessment Guidelines for Noncancer Health Effects, ECAO-CIN-538, November.

US EPA. 1993. "IRIS record for manganese (CASRN 7439-96-5)." Accessed on December 16, 2010 at http://www.epa.gov/ngispgm3/iris/subst/0373.htm.

US EPA. 1994. "Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry." Environmental Criteria and Assessment Office, EPA-600/8-90/066F. Accessed on September 30, 2008 at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993, October.

US EPA. 2002. "A Review of the Reference Dose and Reference Concentration Processes (Final)." Risk Assessment Forum, Reference Dose/Reference Concentration (RfD/RfC) Technical Panel, EPA/630-P-02/002F. Accessed on May 21, 2003 at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=55365 192p.F, December.

Webster, TF. 2007. "Bias magnification in ecologic studies: A methodological investigation." *Environ. Health.* 6:17. Accessed on February 1, 2010 at http://www.ehjournal.net/content/6/1/17.

Winder, BD; Salmon, AG; Marty, MA. 2010. "Inhalation of an essential metal: Development of reference exposure levels for manganese." *Regul. Toxicol. Pharmacol.* 57(2-3):195-199.

Yoon, M; Nong, A; Clewell, HJ; Taylor, MD; Dorman, DC; Andersen, ME. 2009a. "Evaluating placental transfer and tissue concentrations of manganese in the pregnant rat and fetuses after inhalation exposures with a PBPK model." *Toxicol. Sci.* 112(1):44-58.

Yoon, M; Nong, A; Clewell, HJ; Taylor, MD; Dorman, DC; Andersen, ME. 2009b. "Lactational transfer of manganese in rats: Predicting manganese tissue concentration in the dam and pups from inhalation exposure with a pharmacokinetic model." *Toxicol. Sci.* 112(1):23-43.

Young, T; Myers, JE; Thompson, ML. 2005. "The nervous system effects of occupational exposure to manganese - measured as respirable dust - in a South African manganese smelter." *Neurotoxicology.* 26(6):993-1000.

Table A.1
Chronic Inhalation Manganese Occupational Studies Published in or After 1992 (from Bailey *et al.*, 2009)

Reference	Location	Exposed Population (n)	Non-exposed Population (n)	Mean Exposure Duration (years)	Neurological Tests Employed	NOAEL ($\mu g/m^3$)	LOAEL ($\mu g/m^3$)	Findings Statistically Significantly Associated with Mn
Study used as basis of current USEPA IRIS RfC								
Roels *et al.* (1992)	Belgium	Dry alkaline battery workers (92)	Polymer processing factory workers (101)	5.3	• Visual reaction time • Hand-eye coordination • Hand steadiness • Audio-verbal short term memory	NA	Geometric Mean (SD) Respirable Mn: 150 (Lifetime Integrated Exposure of 793 $\mu g/m^3$ / 5.3 years) Personal sampler	• Visual reaction time • Hand-eye coordination • Hand steadiness
COHORT 1								
Chia *et al.* (1993)	Singapore	Milling plant baggers (17)	Hospital housekeeping workers (17)	7.4	• Digit span • Santa Ana dexterity test • Digit symbol test • Benton visual retention test • Pursuit aiming test • Finger tapping • Trail making test	NA	Mean total Mn (95% CI): 1,590 (1,190-1,990) Personal sampler	• Motor speed • Visual scanning • Visuomotor coordination • Visuomotor and response speed • Visuomotor coordination and steadiness

COHORT 2								
Mergler *et al.* (1994)	Quebec	Workers at ferro/silico manganese plant (115)	Workers from neighboring plants (145)	16.7	• Motor functions • Sensory functions • Speech initiation and regulation • Attention, concentration, and memory • Cognitive flexibility • Profile of mood states	NA	Arithmetic mean respirable Mn: 122 Personal and stationary samplers	• Emotional state • Motor functions • Cognitive flexibility • Olfactory perception threshold
Bouchard *et al.* (2006a,b)	Follow-up of Mergler *et al.* (1994) cohort SW Quebec	Former workers from ferro/silico manganese plant (77)	Workers from neighboring plants (81)	15.7	• Neuropsychiatric symptoms (brief symptom inventory) • Global indices of distress • Neurobehavioral tests (Motor Scale of the Luria-Nebraska Neuropsychological Battery, finger-tapping, dynamometer, Nine-Hole Hand Steadiness, Cancellation H, Trail Making A&B, Stroop color-word test, digit span, delayed word recall, symbol digit modalities test) • Profile of mood states	NA	Arithmetic mean respirable Mn: 122 Personal and stationary samplers	• Depression and anxiety • Poorer scores on the Luria Motor Scale, the Hand Steadiness Test, and the color-word trial of the Stroop Color-Word test as well as the Confusion-Bewilderment POMS scale

COHORT 3								
Gibbs *et al.* (1999)	Northern Mississippi	Alkaline battery plant workers with recent (63) and/or historical (12) exposure	Pigment-grade titanium dioxide plant workers (73) and sodium chlorate production facility workers (at alkaline battery plant) (2)	12.7	• Hand/eye coordination • Hand steadiness • Complex reaction time • Rapidity of motion • Steadiness • Tap time	Arithmetic mean (SD) respirable Mn: 66 (59) Personal sampler	NA	None
COHORT 4								
Lucchini *et al.* (1995)	Italy	Male workers from Italian ferro-alloy plant (58) during forced cessation of work (1-42 days). High exposure (19), medium exposure (19), low exposure (20)	None	13.8 (high) 11.8 (medium) 12.9 (low)	• Simple reaction time • Shapes comparison • Additions • Symbol digit • Finger tapping • Digit span	None Range of geometric means (over 10 years) total Mn: 124-319 Personal and stationary samplers	Range of geometric means (over 10 years) total Mn: 270-1,590 Personal and stationary samplers	• Additions • Symbol digit • Finger tapping • Digit span

Lucchini *et al.* (1999)	Follow-up of Lucchini *et al.* (1995) Italy	Ferro-alloy male workers (61)	Maintenance and auxiliary workers from a local hospital (87)	15.2	• Addition, digit span, finger tapping, symbol digit • Motor tasks (open-closed hand tests, thumb-finger touch tests) • Postural tremor • Coordination (hand pronation/supination, reaction time) • Symptoms	NA	Geometric mean total Mn: 96 $\mu g/m^3$ (Geomean Cumulative Exposure Index of 1,113 $\mu g/m^3$ from mid group / geomean of 11.51 years) Personal and stationary samplers	• Irritability, loss of equilibrium and rigidity • Symbol digit, finger tapping, and digit span tests
COHORT 5								
Crump and Rousseau (1999)[a]	Belgium	Manganese oxide workers (114)	Chemical Plant (104)	14	• Short-term memory • Hand-eye coordination • Hand steadiness • Visual reaction time	NA	Median total Mn: 970[b] Personal sampler	None

COHORT 6								
Deschamps *et al.* (2001)	France	Enamels production workers (138)	Technicians from public service employers and laborers from local municipal operations (137)	19.9	• Sensory and motor exam of cranial nerves • Fine-touch, motor, and sensory exam of power of all main muscle groups • Reflex test • Cerebellar abnormalities • Tests of domains of speech regulation and initiation, attention, concentration, and memory, cognitive flexibility, and affect • Questionnaire for neuropsychological status	Arithmetic mean (SD) respirable Mn: 57 (84) Personal sampler	NA	The visual gestalt test score was higher in workers exposed to Mn for 11-15 years, but the authors attribute this to the higher technical skills of this group of six workers. This is supported by a lack of dose-response relationship, as no statistically significant effects were noted in the four people exposed 16-19 years or the 69 people exposed for 20+ years.

COHORT 7								
Bast-Pettersen *et al.* (2004)	Not stated	Mn alloy plant workers (100)	Silicon and microsilica plant and titanium dioxide slag and pig iron plant workers (100)	20.2	• Cognitive functions (Wechsler's adult intelligence scale, digit symbol, trail making test, Stroop test) • Motor tests (hand steadiness/tremor/Klove -Matthews Static readiness test, TREMOR test) • Motor speed/grip strength (finger tapping, foot tapping, dynamometer, grooved pegboard, CATSYS, Luria-Nebraska thumb-finger touch, simple reaction time, hand eye coordination)	NA	Arithmetic Mean (range) respirable Mn: 64 (3-356) Personal sampler	• Postural tremor in visually guided tremor tests • Increased duration of contacts • Larger frequency dispersion of tremor • Tremor increased in exposed smokers *vs.* non-smokers

COHORT 8								
Young *et al.* (2005) [Note: Myers *et al.* (2003) observed similar results in the same cohort based on total manganese concentrations]	South Africa	Manganese smelter workers (509)	Electrical assembly plant workers (67)	18.2	• Digit-span (forward and backward), digit symbol, Santa Ana • Mean reaction time, tapping dominant and non-dominant hand, endurance • CATSYS, tremor, and sway • Luria-Nebraska test	Median (range) respirable Mn: 58 (3-510) Exposure indices attributed or interpolated from 98 personal samplers	NA	Statistically significant associations observed for almost all neurological tests. These occurred primarily with concentrations < 100 $\mu g/m^3$, above which the relationships were "flat." Thus, these effects are likely not to be treatment-related.

[a] *Study of the same cohort of Mn-oxide salt workers as that in Roels et al. (1987).*
[b] *From Roels et al. (1987), as presented in IRIS.*

Table A.2
Current and Proposed Mn Inhalation Toxicity Criteria

Agency	Exposure Period	Point of Departure x HEC Conversion[a]	Uncertainty Factors	Value ($\mu g/m^3$)
US EPA (1993) (current)	Chronic Reference Concentration (RfC)	150 $\mu g/m^3$ LOAEL x 5/7 days x 10/20 m^3/day = 50 $\mu g/m^3$ (Roels *et al.*, 1992)	10 (intraspecies) 10 (database limitations: Mn species; subchronic study; lack of developmental data) 10 (use of a LOAEL) 1000 (TOTAL)	0.05
ATSDR (2000) (current)	Chronic Minimal Risk Level (MRL)	74 $\mu g/m^3$ $BMCL_{10}$ x 5/7 days x 8/24 h/day = 18 $\mu g/m^3$ (Roels *et al.*, 1992)	10 (intraspecies) 10 (database limitations: Mn species; lack of developmental and reproductive data) 5 (sensitivity children) 500 (TOTAL)	0.04
ATSDR (2008) (draft)	Chronic Minimal Risk Level (MRL)	142 $\mu g/m^3$ $BMCL_{10}$ x 5/7 days x 8/24 h/day = 33 $\mu g/m^3$ (Roels *et al.*, 1992)	10 (intraspecies) 10 (database limitations: Mn species; sensitivity to children) 100 (TOTAL)	0.3
California EPA (OEHHA, 2008) (draft)	Chronic Reference Exposure Level (REL)	72 $\mu g/m^3$ $BMCL_{05}$ x 5/7 days x 10/20 m^3/day = 26 $\mu g/m^3$ (Roels *et al.*, 1992)	3 (subchronic study) 100 (intraspecies: 10 for toxicokinetic and 10 for toxicodynamic differences) 300 (TOTAL)	0.09
Bailey *et al.* (2009) (proposed)	Chronic Reference Concentrations (RfC)	60 $\mu g/m^3$ NOAEL x 5/7 days x 10/20 m^3/day = 21 $\mu g/m^3$ (Gibbs *et al.*, 1999; Deschamps *et al.*, 2001; Young *et al.*, 2005)	10 (intraspecies)	2
		200 $\mu g/m^3$ $BMCL_{10}$ x 5/7 days x 10/20 m^3/day = 71 $\mu g/m^3$ (Clewell *et al.*, 2003)	10 (intraspecies)	7

[a] *Human Equivalent Concentration (HEC) determined by Agency*

Appendix B

Resume of Dr. Barbara D. Beck

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Barbara D. Beck, Ph.D., DABT, FATS
Principal
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Areas of Expertise

Risk assessment, exposure assessment, toxicology, metals, inhaled pollutants, soil contaminants, historical knowledge of toxicology.

Education & Certifications

Ph.D., Molecular Biology and Microbiology, Tufts University, 1976.

A.B., Biology, Bryn Mawr College, 1968.

Diplomate of the American Board of Toxicology, 1988; recertified 1994, 1999, 2004, 2009.

Fellow, Academy of Toxicological Sciences, 2002 to Present.

Member, UK Register of Toxicologists, 2004; recertified 2007, 2009.

President, Academy of Toxicological Sciences, July 1, 2009 to June 30, 2010.

Professional Experience

1987 – Present GRADIENT, Cambridge, MA
Principal. Environmental consulting practice includes evaluation of chemical toxicity, health risk assessment for cancer and non-cancer endpoints, review of animal toxicology studies, and multi-media assessment of exposure to environmental chemicals. Special emphasis on metals and inhaled chemicals.

1985 – Present HARVARD SCHOOL OF PUBLIC HEALTH, Boston, MA
Visiting Scientist in Toxicology.

1985 – 1987 REGION I ENVIRONMENTAL PROTECTION AGENCY, Boston, MA
Regional Expert in Toxicology and Supervisory Scientist, Air Toxics Staff. Performed risk assessments for toxic air pollutants. General staff responsibilities included air impacts at waste sites, state air toxic programs, and US EPA radiation programs.

1979 – 1985 HARVARD SCHOOL OF PUBLIC HEALTH, Cambridge, MA
Research Associate in Environmental Science and Physiology and Fellow in Interdisciplinary Programs in Health. Developed short-term animal bioassay for pulmonary toxicants. Editor and author of monograph on variations in susceptibility to inhaled pollutants for both cancer and non-cancer endpoints.

1978 – 1979 TUFTS UNIVERSITY SCHOOL OF MEDICINE, Boston, MA
Instructor in Protein Chemistry. Isolated phagocytosis inhibiting factor from immunoglobulin of individuals with inherited susceptibility to bacterial infections.

1977 – 1978 HARVARD UNIVERSITY, Cambridge, MA
Postdoctoral Fellow in Biology. Researched novel properties of bacterial protein elongation factor, EF-Tu, relevant to possible role as a structural protein.

1975 – 1976 UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, Worcester, MA
Postdoctoral Fellow in Microbiology. Isolated and analyzed messenger RNA from slime molds. Initiated project on elongation factor, EF-Tu.

- Mid-America Course in Toxicology, 1988.
- Pulmonary Pathophysiology, University of Vermont Medical School, 1979.

Note I omitted pages 2 through 27 of the good Drs. resume.